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NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	MAR 31	IFICDB, IFIPAT, and IFIUDB enhanced with new custom IPC display formats
NEWS 3	MAR 31	CAS REGISTRY enhanced with additional experimental spectra
NEWS 4	MAR 31	CA/CAplus and CASREACT patent number format for U.S. applications updated
NEWS 5	MAR 31	LPCI now available as a replacement to LDPCI
NEWS 6	MAR 31	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 7	APR 04	STN AnaVist, Version 1, to be discontinued
NEWS 8	APR 15	WPIDS, WPINDEX, and WPIX enhanced with new predefined hit display formats
NEWS 9	APR 28	EMBASE Controlled Term thesaurus enhanced
NEWS 10	APR 28	IMSRESEARCH reloaded with enhancements
NEWS 11	MAY 30	INPAFAMDB now available on STN for patent family searching
NEWS 12	MAY 30	DGENE, PCTGEN, and USGENE enhanced with new homology sequence search option
NEWS 13	JUN 06	EPFULL enhanced with 260,000 English abstracts
NEWS 14	JUN 06	KOREAPAT updated with 41,000 documents
NEWS 15	JUN 13	USPATFULL and USPAT2 updated with 11-character patent numbers for U.S. applications
NEWS 16	JUN 19	CAS REGISTRY includes selected substances from web-based collections
NEWS 17	JUN 25	CA/CAplus and USPAT databases updated with IPC reclassification data
NEWS 18	JUN 30	AEROSPACE enhanced with more than 1 million U.S. patent records
NEWS 19	JUN 30	EMBASE, EMBAL, and LEMBASE updated with additional options to display authors and affiliated organizations
NEWS 20	JUN 30	STN on the Web enhanced with new STN AnaVist Assistant and BLAST plug-in
NEWS 21	JUN 30	STN AnaVist enhanced with database content from EPFULL
NEWS 22	JUL 28	CA/CAplus patent coverage enhanced
NEWS 23	JUL 28	EPFULL enhanced with additional legal status information from the epoline Register
NEWS 24	JUL 28	IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
NEWS 25	JUL 28	STN Viewer performance improved
NEWS 26	AUG 01	INPADOCDB and INPAFAMDB coverage enhanced

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,

Updated Search

AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS LOGIN Welcome Banner and News Items
NEWS IPC8 For general information regarding STN implementation of IPC 8

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FILE 'HOME' ENTERED AT 11:38:53 ON 11 AUG 2008

=> file hcaplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 0.21 0.21

FILE 'HCAPLUS' ENTERED AT 11:39:04 ON 11 AUG 2008
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FILE COVERS 1907 - 11 Aug 2008 VOL 149 ISS 7
FILE LAST UPDATED: 10 Aug 2008 (20080810/ED)

HCAplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s raf () kinase? () inhib?
7994 RAF
102 RAFS
8070 RAF
(RAF OR RAFS)
336856 KINASE?
2062505 INHIB?

Updated Search

```
L1         339 RAF (W) KINASE? (W) INHIB?

=> s l1 and breast () cancer?
         88751 BREAST
           750 BREASTS
         88982 BREAST
                 (BREAST OR BREASTS)
        387815 CANCER?
         56200 BREAST (W) CANCER?
L2          10 L1 AND BREAST (W) CANCER?

=>

=> s l2 and review/dt
       2170969 REVIEW/DT
L3           2 L2 AND REVIEW/DT

=> d l3, ibib abs hitstr, 1-2

L3   ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2003:736198  HCAPLUS
DOCUMENT NUMBER:         139:301125
TITLE:                   BAY-43-9006(Bayer/Onyx)
AUTHOR(S):               Lee, John T.; McCubrey, James A.
CORPORATE SOURCE:        Department of Microbiology and Immunology, Brody
                         School of Medicine at East Carolina University,
                         Greenville, NC, 27858-4353, USA
SOURCE:                  Current Opinion in Investigational Drugs (Thomson
                         Current Drugs) (2003), 4(6), 757-763
                         CODEN: COIDAZ; ISSN: 1472-4472
PUBLISHER:               Thomson Current Drugs
DOCUMENT TYPE:           Journal; General Review
LANGUAGE:                English
AB   A review.  Bayer and Onyx are developing BAY-43-9006, an oral cytostatic
     Raf kinase inhibitor for the potential
     treatment of colorectal and breast cancers,
     hepatocellular carcinoma and non-small-cell lung cancer, in addition to acute
     myelogenous leukemia, myelodysplastic syndrome and other cancers.  A US
     IND was filed in May 2000 and by Feb. 2003 BAY-43-9006 was in phase II
     trials, with phase III trials expected to begin later in 2003.
REFERENCE COUNT:         41    THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3   ANSWER 2 OF 2  HCAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2003:72813  HCAPLUS
DOCUMENT NUMBER:         139:254471
TITLE:                   Integration of Signal Transduction Inhibitors with
                         Endocrine Therapy: An Approach to Overcoming Hormone
                         Resistance in Breast Cancer
AUTHOR(S):               Johnston, Stephen R. D.; Head, Julia; Pancholi, Sunil;
                         Detre, Simone; Martin, Lesley-Ann; Smith, Ian E.;
                         Dowsett, Mitch
CORPORATE SOURCE:        Departments of Medicine and Academic Biochemistry,
                         Royal Marsden Hospital and Institute of Cancer
                         Research, London, SW3 6JJ, UK
SOURCE:                  Clinical Cancer Research (2003), 9(1, Pt. 2),
                         524S-532S
                         CODEN: CCREF4; ISSN: 1078-0432
```

PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Recent evidence suggests that common mol. adaptations occur during resistance to both tamoxifen and estrogen deprivation that use various signal transduction pathways, often involving cross-talk with a retained and functional estrogen receptor (ER) protein. There appear to be several different levels at which this cross-talk may occur, including peptide growth factor signaling via the type 1 tyrosine kinase growth factor receptor family [epidermal growth factor receptor (EGFR) and HER2], which may become up-regulated during endocrine treatment, ultimately being harnessed by cells to allow them hormone-independent growth. ER may remain involved in cell growth with ligand-independent phosphorylation and activation via different intracellular mitogen-activated protein kinases. ER may also become involved in non-nuclear estrogen-dependent signaling via interaction with the phosphatidylinositol 3'-kinase/Akt cell survival pathway or may interact with the stress-activated protein kinase/c-Jun-NH2-terminal kinase pathway. Understanding these mechanisms will permit the optimal integration of new signal transduction inhibitors (STIs) into breast cancer therapy. Preclin.
approaches that have shown promise include the use of EGFR tyrosine kinase inhibitors for hormone-resistant breast cancer cells
that are dependent on either EGFR or HER2 signaling. Likewise, farnesyl transferase inhibitors, mitogen-activated protein kinase inhibitors, and cell cycle inhibitors have all shown activity in exptl. breast cancer models. Emerging data suggest that STIs may be more effective when given in combination with endocrine therapy either to overcome resistance or to prevent/delay emergence of the resistance phenotype. Clin. trials are in progress to determine the safety and optimal schedule for each of the various STIs, and studies of STIs in combination with aromatase inhibitors have commenced in breast cancer to see whether the therapeutic response to endocrine therapy can be enhanced further.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 11:38:53 ON 11 AUG 2008)

FILE 'HCAPLUS' ENTERED AT 11:39:04 ON 11 AUG 2008
L1 339 S RAF () KINASE? () INHIB?
L2 10 S L1 AND BREAST () CANCER?
L3 2 S L2 AND REVIEW/DT

=> s l2 not l3
L4 8 L2 NOT L3

=> d l4, ibib abs hitstr, 1-8

L4 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:782528 HCAPLUS
TITLE: Protein alterations in infiltrating ductal carcinomas of the breast as detected by nonequilibrium pH gradient electrophoresis and mass spectrometry
AUTHOR(S): Kabbage, Maria; Chahed, Karim; Hamrita, Bechr; Guillier, Christelle Lemaitre; Trimeche, Mounir;

Remadi, Sami; Hoebeke, Johan; Chouchane, Lotfi
CORPORATE SOURCE: Laboratoire d'Immuno-Oncologie Moleculaire, Faculte de Medecine de Monastir, Monastir, 5019, Tunisia
SOURCE: Journal of Biomedicine and Biotechnology (2008) No pp. given
CODEN: JBBOAJ; ISSN: 1110-7251
URL: http://www.hindawi.com/GetArticle.aspx?doi=10.1155/2008/564127
PUBLISHER: Hindawi Publishing Corp.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Improvement of breast-cancer detection through the identification of potential cancer biomarkers is considered as a promising strategy for effective assessment of the disease. The current study has used nonequil. pH gradient electrophoresis with subsequent anal. by mass spectrometry to identify protein alterations in invasive ductal carcinomas of the breast from Tunisian women. We have identified multiple protein alterations in tumor tissues that were picked, processed, and unambiguously assigned identities by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF). The proteins identified span a wide range of functions and are believed to have potential clin. applications as cancer biomarkers. They include glycolytic enzymes, mol. chaperones, cytoskeletal-related proteins, antioxydant enzymes, and immunol. related proteins. Among these proteins, enolase 1, phosphoglycerate kinase 1, deoxyHb, Mn-superoxyde dismutase, α-B-crystallin, HSP27, Raf kinase inhibitor protein, heterogeneous nuclear ribonucleoprotein A2/B1, cofilin 1, and peptidylprolyl isomerase A were overexpressed in tumors compared with normal tissues. In contrast, the IGHG1 protein, the complement C3 component C3c, which are two newly identified protein markers, were downregulated in IDCA tissues.

L4 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:771147 HCAPLUS
DOCUMENT NUMBER: 149:112579
TITLE: Compositions comprising indolocarbazole K252a derivatives and methods for the treatment of cancer
INVENTOR(S): Roder, Hanno
PATENT ASSIGNEE(S): Tautatis, Inc., USA
SOURCE: PCT Int. Appl., 91pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008076394	A1	20080626	WO 2007-US25692	20071214

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2006-875013P P 20061214

AB The present invention relates to the use of specific compds. related to the indolocarbazole K252a that are inhibitors of a combination of growth-related pathways, for the preparation of pharmaceutical compns. for the treatment of various forms of cancer. Thus, human estrogen receptor and EGF receptor neg. MDA-MB-231 (HTB 26) breast cancer cell line were cultured in McCoy's 5A medium containing L-glutamine, 2.2 g/l NaHCO3 and 5 % fetal calf serum; after 2-3 days the culture medium was removed by suction and replaced by fresh medium (200 gl/well) containing varying concns. of a K252a derivative (Compound 1) or vehicle (0.5 % DMSO); Compound 1 was added as 1000-fold concentrated feed solns. and exhibited high biol. activity.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:746290 HCAPLUS

TITLE: Effects of Raf Kinase Inhibitor Protein Expression on Metastasis and Progression of Human Epithelial Ovarian Cancer

AUTHOR(S): Li, Hong Zhao; Wang, Yue; Gao, Yan; Shao, Jie; Zhao, Xiu Lan; Deng, Wei Min; Liu, Yi Xin; Yang, Jie; Yao, Zhi

CORPORATE SOURCE: Department of Immunology, Tianjin Medical University, Tianjin, Peop. Rep. China

SOURCE: Molecular Cancer Research (2008), 6(6), 917-928 CODEN: MCROC5; ISSN: 1541-7786

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Loss of function of metastasis suppressor genes is an important step in the progression to a malignant tumor type. Studies in cell culture and animal models have suggested a role of Raf kinase inhibitor protein (RKIP) in suppressing the metastatic spread of prostate cancer, breast cancer, and melanoma cells. However, the function of RKIP in ovarian cancer (OVCA) has not been reported. To explore the potential role of RKIP in epithelial OVCA metastasis, we detected the expression levels of RKIP protein in tissue samples from patients with epithelial OVCA. Consequently, the expression of RKIP is reduced in the poorly differentiated OVCA than in the well-differentiated and moderately differentiated OVCA. In addition, in vitro cell invasion assay indicated that the RKIP expression was inversely associated with the invasiveness of five OVCA cell lines. Consistent with this result, the cell proliferation, anchorage-independent growth, cell adhesion, and invasion were decreased in RKIP overexpressed cells but increased in RKIP down-regulated cells. Further investigation indicated that RKIP inhibited OVCA cell proliferation by altering cell cycle progression rather than promoting apoptosis. Furthermore, the overexpression of RKIP suppressed the ability of human OVCA cells to metastasize when the tumor cells were transplanted into nude mice. Our data show the effect of RKIP on the proliferation, migration, or adhesion of OVCA cells. These results indicate that RKIP is also a metastasis suppressor gene of human epithelial OVCA. (Mol Cancer Res 2008;6(6):917-28).

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:341796 HCAPLUS
DOCUMENT NUMBER: 144:465456
TITLE: Gene expression signatures and biomarkers of noninvasive and invasive breast cancer cells: comprehensive profiles by representational difference analysis, microarrays and proteomics
AUTHOR(S): Nagaraja, G. M.; Othman, M.; Fox, B. P.; Alsaber, R.; Pellegrino, C. M.; Zeng, Y.; Khanna, R.; Tamburini, P.; Swaroop, A.; Kandpal, R. P.
CORPORATE SOURCE: Department of Biological Sciences, Fordham University, Bronx, NY, USA
SOURCE: Oncogene (2006), 25(16), 2328-2338
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDA-MB-231). The transcript profiles were first analyzed by a modified protocol for representational difference anal. (RDA) of cDNAs between MCF7 and MDA-MB-231 cells. The majority of genes identified by RDA showed nearly complete concordance with microarray results, and also led to the identification of some differentially expressed genes such as lysyl oxidase, copper transporter ATP7A, EphB6, RUNX2 and a variant of RUNX2. The altered transcripts identified by microarray anal. were involved in cell-cell or cell-matrix interaction, Rho signaling, calcium homeostasis and copper-binding/sensitive activities. A set of nine genes that included GPCR11, cadherin 11, annexin A1, vimentin, lactate dehydrogenase B (upregulated in MDA-MB-231) and GREB1, S100A8, amyloid β precursor protein, claudin 3 and cadherin 1 (downregulated in MDA-MB-231) were sufficient to distinguish MDA-MB-231 from MCF7 cells. The downregulation of a set of transcripts for proteins involved in cell-cell interaction indicated these transcripts as potential markers for invasiveness that can be detected by methylation-specific PCR. The proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles. Antisense knockdown of selected transcripts led to inhibition of cell proliferation that was accompanied by altered proteomic profiles. The proteomic profiles of antisense transfectants suggest the involvement of peptidyl-prolyl isomerase, Raf kinase inhibitor and 80 kDa protein kinase C substrate in mediating the inhibition of cell proliferation.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1125462 HCAPLUS
DOCUMENT NUMBER: 143:405907
TITLE: Preparation of imidazole derivatives as inhibitors of tyrosine kinases and Raf kinases
INVENTOR(S): Hoelzemann, Guenter; Crassier, Helene; Jonczyk, Alfred; Staehle, Wolfgang; Sutter, Arne; Rautenberg, Wilfried; Mitjans, Francesc; Rosell-Vives, Elisabet; Adan, Jaume; Soler, Marta

PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: Ger. Offen., 37 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 102004015099	A1	20051020	DE 2004-102004015099	20040329
AU 2005231907	A1	20051020	AU 2005-231907	20050315
CA 2561585	A1	20051020	CA 2005-2561585	20050315
WO 2005097755	A2	20051020	WO 2005-EP2746	20050315
WO 2005097755	A3	20060309		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1761503	A2	20070314	EP 2005-716076	20050315
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LV				
CN 1938282	A	20070328	CN 2005-80010619	20050315
BR 2005008881	A	20070911	BR 2005-8881	20050315
JP 2007530609	T	20071101	JP 2007-505422	20050315
IN 2006KN02398	A	20070525	IN 2006-KN2398	20060824
MX 2006PA10968	A	20061116	MX 2006-PA10968	20060925
US 20070225347	A1	20070927	US 2007-593295	20070111

PRIORITY APPLN. INFO.: DE 2004-102004015099A 20040329
WO 2005-EP2746 W 20050315
OTHER SOURCE(S): MARPAT 143:405907
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1, R2, R3, R4 and R5 independently = H, OH, NH2, etc. or two neighboring R1, R2, R3, R4 and R5 together may form -O-CH2-CH2-, -O-CH2-O- or -O-CH2-CH2-O-; R6 and R7 independently = H, OH, CN, etc.; R8 = CN, COOH, CONH2, etc.; R9, R10 and R11 independently = H or A; A = (un)substituted alkyl; X and X1 independently = NH or missing] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of tyrosine kinases and Raf kinases. Thus, e.g., II was prepared by coupling of 2-methoxy-5-trifluoromethylaniline with 4-nitrophenyl chloroformate followed by deprotection and subsequent cyclization using 2-amino-2-cyanoacetamide. The inhibitory activity of I towards VEGF-receptor kinase was evaluated using scintillation assays and it was revealed that compds. of the invention displayed kinase inhibitory activity (no data). I as inhibitors of tyrosine kinases and Raf kinases

should prove useful in the treatment of diseases such as but not limited to lung cancer, breast cancer and arthritis. Pharmaceutical compns. comprising I are disclosed.

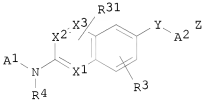
L4 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:420302 HCAPLUS
DOCUMENT NUMBER: 143:259602
TITLE: Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumours
AUTHOR(S): Awada, A.; Hendlisz, A.; Gil, T.; Bartholomeus, S.; Mano, M.; de Valeriola, D.; Strumberg, D.; Brendel, E.; Haase, C. G.; Schwartz, B.; Piccart, M.
CORPORATE SOURCE: Jules Bordet Institute, Brussels, 1000, Belg.
SOURCE: British Journal of Cancer (2005), 92(10), 1855-1861 CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB BAY 43-9006 is a novel dual-action Raf kinase and vascular endothelial growth factor receptor (VEGFR) inhibitor that targets tumor cell proliferation and tumor angiogenesis. This Phase I study was undertaken to determine the safety profile, maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), pharmacokinetics, and tumor response profile of oral BAY 43-9006 in patients with advanced, refractory solid tumors. BAY 43-9006 was administered daily for repeated cycles of 21 days on/7 days off. A total of 44 patients were enrolled at doses from 50 to 800 mg b.i.d. Pharmacokinetic profiles of BAY 43-9006 in plasma were determined during the first treatment cycle. The most frequently reported adverse events over multiple cycles were gastrointestinal (75%), dermatol. (71%), constitutional (68%), pain (64%), or hepatic (61%) related. A MTD of 400 mg b.i.d. BAY 43-9006 was defined. BAY 43-9006 was absorbed rapidly; steady-state conditions were reached within 7 days. BAY 43-9006 exposure increased nonproportionally with increasing dose. In all, 32 patients were evaluated for tumor response: 15 patients showed tumor progression, 16 patients experienced stable disease (>6 mo in eight patients), and one patient with renal cell carcinoma achieved a partial response. BAY 43-9006 given for 21 days with 7 days off treatment was safe, well tolerated, and showed antitumor activity.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:349005 HCAPLUS
DOCUMENT NUMBER: 142:411374
TITLE: Preparation of 2,6-disubstituted quinazolines, quinoxalines, quinolines and isoquinolines and their use as inhibitors of Raf kinase
INVENTOR(S): Ramurthy, Savithri; Renhowe, Paul A.; Subramanian, Sharadha
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 42 pp. CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050085482	A1	20050421	US 2004-966358	20041015
AU 2004281154	A1	20050428	AU 2004-281154	20041015
CA 2542329	A1	20050428	CA 2004-2542329	20041015
WO 2005037285	A1	20050428	WO 2004-US34185	20041015
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1680122	A1	20060719	EP 2004-795363	20041015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN 1882345	A	20061220	CN 2004-80030549	20041015
JP 2007509059	T	20070412	JP 2006-535368	20041015
MX 2006PA03607	A	20060605	MX 2006-PA3607	20060330
KR 2007029110	A	20070313	KR 2006-707130	20060413
IN 2006KN01069	A	20070420	IN 2006-KN1069	20060425
PRIORITY APPLN. INFO.:			US 2003-511851P P	20031016
			WO 2004-US34185 W	20041015

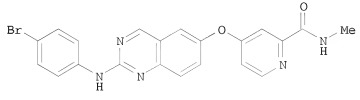
OTHER SOURCE(S): CASREACT 142:411374; MARPAT 142:411374

GI



I

II



III

AB The title compds. I [X1, X2 = N, CH, provided that at least one of X1 and X2 = N; Y = O, S, CH2, etc.; Z = II, NR6R7, NR5C(:O)R8, NR5C(:S)R8, NR5AA (wherein AA = (un)substituted amino acid); A1 = (un)substituted alkyl, cycloalkyl, heterocycloalkyl, aryl, etc.; A2 = (un)substituted (hetero)aryl; R1 = O or H, and R2 = NR6R7; or R1 is taken together with R2 to form (un)substituted heterocycloalkyl or heteroaryl group; R3 = R31 = H, halo, alkyl, or alkoxy; R4 = H, OH, (un)substituted alkyl; R5 = H, (un)substituted alkyl, alkoxyalkyl, etc.; R6, R7 = H, (un)substituted

alkyl, alkoxy, alkoxyalkyl, etc.; or R6 and R7 are taken together to form (un)substituted heterocyclyl or heteroaryl; and R8 = (un)substituted alkyl, alkenyl, alkynyl, alkoxy, etc.; X3 is not defined], useful for inhibition of Raf kinase activity in a human or animal, were prepared E.g., a multi-step synthesis of III, starting from 5-hydroxy-2-nitrobenzaldehyde, was given. The exemplified compds. I were shown to have a raf kinase inhibitory activity at an IC50 of less than 5 μM. The new compds. I may be used either alone or in combination with at least one addnl. agent for the treatment of a Raf kinase mediated disorder, such as cancer. The pharmaceutical compns. comprising the compound I are disclosed.

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TITLE: RKIP Sensitizes Prostate and Breast Cancer Cells to Drug-induced Apoptosis

AUTHOR(S): Chatterjee, Devasis; Bai, Yin; Wang, Zhe; Beach, Sandy; Mott, Stephanie; Roy, Rajat; Braastad, Corey; Sun, Yaping; Mukhopadhyay, Asok; Aggarwal, Bharat B.; Darnowski, James; Pantazis, Panayotis; Wyche, James; Fu, Zheng; Kitagwa, Yasuhide; Keller, Evan T.; Sedivy, John M.; Yeung, Kam C.

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AB Cancer cells are more susceptible to chemotherapeutic agent-induced apoptosis than their normal counterparts. Although it has been demonstrated that the increased sensitivity results from deregulation of oncoproteins during cancer development (Evan, G. I., and Vousden, K. H. (2001) Nature 411, 342-348; Green, D. R., and Evan, G. I. (2002) Cancer Cell 1, 19-30), little is known about the signaling pathways leading to changes in the apoptotic threshold in cancer cells. Here we show that low RKIP expression levels in tumorigenic human prostate and breast cancer cells are rapidly induced upon chemotherapeutic drug treatment, sensitizing the cells to apoptosis. We show that the maximal RKIP expression correlates perfectly with the onset of apoptosis. In cancer cells resistant to DNA-damaging agents, treatment with the drugs does not up-regulate RKIP expression. However, ectopic expression of RKIP resensitizes DNA-damaging agent-resistant cells to undergo apoptosis. This sensitization can be reversed by up-regulation of survival pathways. Down-regulation of endogenous RKIP by expression of antisense and small interfering RNA (siRNA) confers resistance on sensitive cancer cells to anticancer drug-induced apoptosis. Our studies suggest that RKIP may represent a novel effector of signal transduction pathways leading to apoptosis and a prognostic marker of the pathogenesis of human cancer cells and tumors after treatment with clin. relevant chemotherapeutic drugs.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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